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99D-1454 '99 AUG 31 A9:36

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

August 25, 1999

Dear Sirs,

Attached please find comments with regard to the draft guidance for industry entitled, "Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products; Chemistry, Manufacturing, and Controls Documentation", written by Guirag Poochikian, Ph.D. published June 2, 1999 in the Federal Register, Docket No. 99D-1454, CDER 98 185.

Pfeiffer GmbH is a leading supplier of nasal spray pumps to the pharmaceutical industry.

The draft guidance significantly influences current and future Pfeiffer pump business with regard to nasal spray drug product development and registration.

If you have any comments or require further clarification contact me directly at (609) 987-0223 Ext. 15.

Mr. Jay Occulto
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Director of Regulatory Affairs

99D-1454

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FDA DRAFT GUIDANCE FOR INDUSTRY:

"NASAL SPRAY AND INHALATION SOLUTION, SUSPENSION AND SPRAY DRUG PRODUCTS"

Review comments from Pfeiffer GmbH

GENERAL OVERVIEW: Pfeiffer is a leading supplier of nasal spray pumps for the pharmaceutical industry. Pfeiffer continuously strives to consistently manufacture nasal spray pumps of known quality and performance. Pfeiffer has taken a proactive approach in working with the FDA and the customer base in order to support the nasal spray drug product approval process in accordance to the recent FDA draft guidance's. It is Pfeiffer's primary intention to meet the guidance's requirements as a manufacturer and to protect the health and safety of the patient. This guidance document significantly affects the development and registration of nasal spray drug products with the FDA. Any excessive tightening of proposed specifications developed on limited drug product batches has direct impact on Pfeiffer business and can add significant risk to the applicant in acceptance of nasal spray pump lots from the supplier. In general, the applicant's drug product regulatory specifications as submitted to the FDA must meet the supplier's approval and must be representative of the supplier's process capability. The applicant, the FDA and the supplier must agree to the regulatory specifications upon approval of the drug product.

348-349	In-vitro performance parameters should be established before initiating critical clinical or bioequivalence studies; "critical" needs to be further defined.
417, 427, 430, 492, 493, 499	The spray discharged from the nosepiece; "nosepiece" is typically referred to as a "nasal actuator".
425	(e.g., stroke length, depression force); "depression" force is typically referred to as "actuation" force.
479	Are important for evaluating the pump and nozzle; "nozzle" is typically referred to as a "nasal actuator".
480	Including the size and the shape of the nozzle; "nozzle" is more appropriately referred to in this statement as a "spray insert".
492	Number of sprays per spray pattern; this statement needs clarification; possibly refers to the "number of sprays per determination".
497	The ratio of the longest to the shortest axis should lie in a specified range, for example, 1 .OO to 1.20; this example is not typical and infers that the spray pattern is close to being concentric in shape; a recommended example is from "1 .OO to 1 .50" that allows for ovality.
499	Spray pattern at different distances, (e.g., two) from the nosepiece; it is strongly recommended to utilize only one distance from the nasal actuator to the collection surface to determine spray pattern In development the applicant can characterize the relationship of spray patterns determined at different distances and then select one optimal distance to assess quality of the drug product.

507	Appropriate control for the droplet size distribution (e.g., 3-4 cut-off values); This example needs clarification and standardization; the recommended format for reporting droplet size distribution should be standardized to include ranges for the percent of droplets less than 10*um*, D(v, 0.1), D(v, 0.5) and D(v, 0.9). The data should be presented as reported directly by the Malvern Mastersizer and not recalculated.
542	Foreign particulates may originate during manufacturing, from formulation components, and, in particular, from the container and closure components; "In particular" suggest inadequate container and closure component quality and the phrase should be deleted making the statement evenly distributed among the potential causes.
800	The word pumps refer to all components that are responsible for metering, aerosolization, and delivery of the formulation; the term "aerosolization" does not apparently apply to mechanical spray pumps. A recommended term may be "atomization".
810	The device should be designed to prevent partial metering of the formulation; mishandling or improper actuation of the multidose nasal spray pump can lead to partial metering of the formulation. Standard nasal spray pumps should be actuated according to the accompanying Patient Instructions utilizing a firm continuous stroke in order to prevent partial metering of the drug formulation.
311	The use of some type of dose counting mechanism is encouraged; recommend the sentence to incorporate the phrase "encouraged to promote patient compliance but not required". What is the specific intention of the guidance and the agency here?
827-832	The identity and concentration of the leachables in the drug product or placebo formulation through the end of the drug product shelf life should be determined; this statement assumes that there are leachables found in the drug product formulation. If there is no measurable amount of extractables determined in either the extractables profile of the container closure components and no measurable amount of leachables determined in the drug product, then what is required in this case for drug product registration? It is recommended that for routine quality assurance the component supplier can monitor the gravimetric extractables of the supplied resin materials upon incoming inspection as a suitable surrogate for drug product performance.
833-839	For ANDA's the applicant may compare the extraction profiles of the container and closure components; what are the registration requirements with regard to extractables if the pump components are found to be identical?
\$50, 851	Source(s) and fabricator(s); definition of "source" needs to provided.
\$54, 855	Schematic engineering drawings of the container, closure and pump components should be included; individual pump component engineering drawings are not made available to the applicant due to proprietary risk to the DMF Holder. The applicant typically receives a pump assembly drawing, an actuator assembly drawing and a basic pump assembly drawing from the supplier with "critical" dimensions as required for registration purposes.

857,872	Composition and quality of the materials of the container, closure and pump components should be included; typically only the general composition of the pump materials and the supplier of the materials is provided to the applicant. The formulation composition of the pump materials is strictly confidential and is contained in the sub-supplier's DMF.
859,860	Control extraction studies and toxicological evaluations; it is recommended for nasal spray pumps the extraction studies and the toxicological evaluations should be a one-time characterization as per USP requirements and not routine evaluations. For nasal spray pumps both material extractables and toxicological evaluations can be referenced in the supplier's DMF. If product specific toxicological issues arise the NDA applicant should address the issue.
391-900	Control extraction studies; it is recommended that these studies should only be necessary for critical components in contact with the drug product. In addition, extraction studies should be performed with appropriate solvents such as water and/or alcohol reflective of the formulation and not highly aggressive solvents.
)24-937	Routine Extraction; it is recommended that routine extraction should not be performed on individual pump components. Gravimetric extractions can be performed on the received raw materials and the correlation to the pump components established during the development process. Current validation studies demonstrate that the production process has no significant impact on the extractables profile of the pump materials. Acceptance specifications for gravimetric extractables can be established and optimized over receipt of several batches of resin. It should be sufficient for the applicant to test the first three lots of pumps to confirm the suppliers test results combined with audits and annual verification of certified test results.
)52	"Actuation force" is not typically a controlled pump performance attribute.
'56	Referenced clinical batches should be defined, such as Phase III when the final package is determined.

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